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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/294,494	04/20/1999	RICHARD LESLIE EDELSON	270425.003	6196

7590 07/28/2002

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 07/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/294,494	EDELSON, RICHARD LESLIE	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-27,46-60,64 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-27,46-60,64 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 07, 2002 has been entered.

Claims 13-27, 46-60 and 64-65 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-27, 46-60 and 64-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising functional dendritic antigen presenting cells derived from monocytes which have been incubated following their treatment comprising exposing the monocytes through a narrow diameter plastic channel during the photopheresis and leukapheresis processes, and a packaged preparation comprising the same, does not reasonably provide enablement for other embodiments of the claims. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing the enhanced photopheresis protocol of the present application resulted in large numbers of mature dendritic cells derived from monocytes and apoptotic T cells in blood samples subjected to photopheresis and incubation for about 22 hours. Applicant further teaches that the centrifugal forces associated with leukapheresis together with an overnight incubation can also induce efficiently a large number of mature dendritic cells from isolating monocytes. Without subjecting to photopheresis, little apoptosis of T cells was observed in the T cell population isolated by leukapheresis. The specification also discloses that a treatment method based on the enhanced photopheresis protocol of the presently claimed invention has been tested in a pilot study involving four cutaneous T-cell lymphoma (CTCL) subjects whose disease had been advancing while on standard photopheresis. Over a twelve-month treatment period, although no subject experienced complete hematologic remissions, previous rapid increases in blood CTCL cells were reversed. There was also a lack of symptomatic infections common in individuals

whose immune systems have been compromised by their CTCL as well as a decrease in the severity and distribution of skin lesions in treated subjects. The evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

As written, the instant claims encompass a composition comprising functional dendritic anigen presenting cells derived from monocytes which have been incubated following their treatment by exposure to any physical pertubation, or by irradiation in the presence of photoactivatable agents that are capable of forming photoadducts with cellular components or by treatment with any DNA binding agent; and a packaged preparation comprising the same composition. The instant specification is not enabled for such a broadly claimed invention. Apart from disclosing irradiation of the monocytes with a photoactivable agent during the photophoresis process or subjecting the monocytes to centrifugal forces associated with leukapheresis, followed by an effective incubation period, a large number of mature dendritic cells were generated, the instant specification offers no guidance for a skilled artisan in the art on how to induce the differentiation of monocytes by any physical pertubation or by any DNA binding agent or by irradiation in the presence of any photoactivatable agent alone. For examples, would any forms of physical perturbation such as centrifugation, vibration, electroporation and others would be effective in inducing the differentiation of monocytes into dendritic antigen presenting cells. There are no specific teachings regarding to the parameters used in other forms of physical perturbation encompassed by the claims for inducing monocyte differentiation into functional dendritic antigen presenting cells. Various

preparations of monocytes known in the art (Garbe et al. (Blood 92, No. 10, Supplement 1, 165a, 1998; Tedder et al.; U.S. Patent No. 5,849,589; Akagawa et al.; Blood 88:4029-4039, 1996) were also subjected to physical pertubation such as centrifugation, washing, pipetting during their isolation, and yet they are not differentiated into functional dendritic cells on plastic cell culture plates unless certain cytokines are also added into the cell cultures. Additionally, would any transcriptional factors, any DNA binding domains, or any small molecule compounds capable of binding DNA including ethedium bromide (all of which are DNA binding agents) are also able of inducing monocytes into functional dendritic antigen presenting cells? The instant specification also explicitly teaches that the simple exposure to ultraviolet light (irradiation) does not seem to play a role in the induction of monocyte differentiation into functional dendritic cells (see the fourth set of bars in Figure 1). Furthermore, it is apparent that the critical feature for the presently claimed invention is the passing of the monocytes through a narrow diameter plastic channel during the photopheresis and leukapheresis processes, and that as the monocytes in the fluid come into contact with the surface of the plastic channel, the monocytes repeatedly adhere to the plastic surface and are sheared from the surface by the force of the fluid flow through the channel, and the forces experienced by the monocytes in this process induce a relatively large number of the monocytes to differentiate into functional dendritic cells as explained by Applicants (see Amendment filed May 07/02 in Paper No. 13, last paragraph of page 3 continues to top of page 4). Therefore, this critical element or feature should be present in the claims. Apart from this disclosed critical feature, the instant specification fails to provide

sufficient guidance for a skilled artisan on how to induce the differentiation of monocytes into functional dendritic cells for a composition as claimed. Nor does the prior art at the effective filing date of the present application provide such guidance. With the lack of sufficient guidance provided by the present specification, it would require undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 102

Claims 13-21 and 64 remain rejected under 35 U.S.C. 102(a) as being anticipated by Garbe et al. (Blood 92, No. 10, Supplement 1, 165a, 1998, PTO-1449 in paper no. 4).

The claims are drawn to a composition comprising functional dendritic antigen presenting cells derived from monocytes which have been incubated following their treatment by at least one of: (1) exposure to physical perturbation, (2) irradiation in the presence of a photoactivatable agent that forms photoadducts with cellular components, or (3) treatment with a DNA binding agent; the same composition further comprising at least one of GM-CSF or IL-4 (claim 20) or the same composition wherein it further comprises at least one selected antigen for presentation by the dendritic cells (claim 21).

Garbe et al. disclose the generation of CD1a+ dendritic cells from adherent cultured peripheral monocytes in the presence of IL-4, GM-CSF and TGFβ under serum-free conditions, and the phenotype of cells obtained after 7 days was determined by flow cytometry (second full paragraph, lines 1-4). Garbe et al. further teach that in the presence of both TGFβ and tetanus toxoid, the generated dendritic cells were less effective to stimulate the proliferation of primed autologous T-cells as compared to dendritic cells being depleted of TGFβ before being matured in the presence of TNF-α (second paragraph, lines 12-16). It is noted that the instant claims are composition by process claims, and the composition comprising differentiated dendritic cells from monocytes under serum-free conditions in the presence of different cytokine combinations taught by Garbe et al. is indistinguishable from that of the present

invention. For this instance, the processes in making the same composition are not given any patentable weight. Furthermore, there is no disclosure of a feature to the claimed composition that distinguishes it from the composition of Garbe et al. Therefore, Garbe et al. anticipate the instant claimed invention.

Responses to Arguments

Applicants' arguments and Dr. Edelson's Declaration related to the above rejection in the Amendment filed on May 07, 2002 in Paper No. 13 (pages 2-7) have been fully considered.

Applicants mainly argued that "Garbe et al. does not teach or suggest a composition in which dendritic cells are formed in a short time and in which the age of the dendritic cells in the composition is relative uniform". Applicants also argued that the cell culturing process of Garbe et al. takes five days instead of 6 to 48 hours in the process of the instant invention, therefore the age of the dendritic cells generated in the process of Garbe et al. varies widely and a composition comprising such dendritic cells is not effective in presenting antigens as the composition containing dendritic cells of the presently claimed invention. Applicants referred Examiner to the data set forth in Table I of the Edelson Declaration to support the above arguments that the composition claimed of the present invention contains more functional dendritic cells, functional dendritic cells of a relatively uniform age as compared to a composition produced by the prior art method, such as that of Garbe. Examiner respectfully finds Applicants' arguments to be unpersuasive for the following reasons.

Firstly, the instant claimed composition is not limited to a composition comprising functional dendritic antigen presenting cells of relatively uniform age, at any particular stage of dendritic cell differentiation. Secondly, there is no factual evidence indicating that the functional dendritic antigen presenting cells in the claimed composition possess any distinct cell markers to distinguish themselves from those in the composition taught by Garbe et al. This is also supported by the data presented in Table I of the Declaration of Dr. Edelson. Thirdly, the observed differences in the percentages of dendritic cell populations set forth in Table I of the Edelson Declaration are between a composition prepared by the method of the presently claimed invention and a composition prepared by a conventional method after 24h of incubation, not after 7 days of culture as taught by Garbe et al. The fact pattern in the Declaration is not the same with respect to the data of Garbe et al. It is known that given a sufficient amount of time, more monocytes will be differentiated into functional dendritic cells. Fourthly, there is nothing in the presented data of Table I in the Edelson Declaration indicating that the age of dendiritic cells is relatively uniform, with 52% of the cells possess CD36 marker, 22% of the cells possess cCD83 marker and 15% of the cells possess mCD83 marker. Furthermore, MPEP 2112.01 clearly states that "If the composition is physically the same, it must have the same properties".

Accordingly, claims 13-21 and 64 remain rejected for the reasons set forth above.

Claims 13-21 and 64 remain rejected under 35 U.S.C. 102(e) as being anticipated by Tedder et al. (U.S. Patent No. 5,849,589).

Tedder et al. disclose a composition comprising induced differentiated monocytes into dendritic cells in the presence of GM-CSF, IL-4 and TNFα (column 2, lines 19-37) at various cultured time periods (at least 5 days; see cols. 5-6). The monocytes are plastic adherent human blood monocytes (col. 2, lines 48-49). Tedder et al. disclose that upon addition of TNFα into GM-CSF and IL-4 cell cultures at day 5, the cells became adherent to the tissue culture plates and 78-95% of the cells became CD83+ within 2-3 days (col. 5, lines 28-31). Furthermore, Tedder et al. teach that the dendritic cells are plated in cultured dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells (column 11, lines 51-57).

As noted above, the instant claims are composition by process claims, and there is no disclosure of a feature to the claimed composition that distinguishes it from the composition of Tedder et al. Therefore, Tedder et al. anticipate the instant claimed invention.

Responses to Arguments

Applicants' arguments and Dr. Edelson's Declaration related to the above rejection in the Amendment filed on May 07, 2002 in Paper No. 13 (pages 2-8) have been fully considered.

Applicants mainly argued that Tedder does not teach or suggest a composition containing dendritic cells produced in a relatively short time in which the age of the dendritic cells is relatively uniform. Examiner respectfully finds Applicants' arguments to be unpersuasive for the same reasons stated in the Response to the arguments related to the Garbe et al. reference. Basically, the instant claimed composition is not limited to a composition comprising functional dendritic antigen presenting cells of relatively uniform age, at any particular stage of dendritic cell differentiation. There is no factual evidence indicating that the functional dendritic antigen presenting cells in the claimed composition possess any distinct cell markers to distinguish themselves from those in the composition taught by Tedder. Thirdly, Tedder clearly showed that 78-95% of the cells became CD83+ within 2-3 days after the addition of TNFα into GM-CSF and IL-4 cell cultures at day 5. Furthermore, MPEP 2112.01 clearly states that "If the composition is physically the same, it must have the same properties".

Accordingly, claims 13-21 and 64 remain rejected for the reasons set forth above.

Claims 13-20 and 64 remain rejected under 35 U.S.C. 102(b) as being anticipated by Akagawa et al. (Blood 88:4029-4039, 1996).

Akagawa et al. disclose the generation of CD1+relB+ dendritic cells from adherent human monocytes in the presence of GM-CSF plus IL-4 in 7 day cell cultures (page 4030, col. 1, under Materials and Methods). The monocyte-derived dendritic cells can be maintained in the terminally differentiation of dendritic cells with TNFα (See abstract and page 4032, column 2, second and third full paragraphs). Since there is no disclosure of a feature to the claimed composition that distinguishes it from the composition of Akagawa et al., the reference anticipates the claimed invention.

Responses to Arguments

Applicants' arguments and Dr. Edelson's Declaration related to the above rejection in the Amendment filed on May 07, 2002 in Paper No. 13 (pages 2-9) have been fully considered.

Applicants mainly argued that Akagawa does not teach or suggest a composition containing an optimum number of functional antigen presenting dendritic cells as the composition of the presently claimed invention nor Akagawa describes the population of dendritic cells expressing the mCD83 cell marker produced by the culturing method. Examiner respectfully finds Applicants' arguments to be unpersuasive for the same reasons stated in the responses related to the cited references of Garbe et al. and Tedder et al. above. It is further noted that there is no recitation of any dendritic cell marker for dendritic antigen presenting cells in the instantly claimed composition.

Accordingly, claims 13-20 and 64 remain rejected for the reasons set forth above.

Claims 13-23 and 64 remain rejected under 35 U.S.C. 102(e) as being anticipated by Cohen et al. (U.S. Patent No. 6,010,905).

The claims are drawn to a composition comprising functional dendritic antigen presenting cells derived from monocytes which have been incubated following their treatment by at least one of: (1) exposure to physical perturbation, (2) irradiation in the presence of a photoactivatable agent that forms photoadducts with cellular components, or (3) treatment with a DNA binding agent.

Cohen et al. teach a preparation of monocytes having increasing the antigen presenting ability including those with the phenotype of an activated myeloid dendritic cell by contacting the monocytes with an agent, preferably a calcium ionophore, which elevates the intracellular calcium concentration to a level sufficient and effective to increase said antigen presenting ability (column 4, lines 13-18, column 5, lines 5-12). Cohen et al. disclose that the same composition further treated with a second agent selected from the group consisting of rhGM-CSF, rhIL-4, rhIL-12, rhIL-2, and rhTNFalpha (column 5, lines 5-12). Cohen et al. also teach contacting the monocytes isolated from the blood of a subject with a cancer with an agent which increases the intracellular calcium concentration, thereby enhancing the antigen presenting ability of the monocytes, then exposing the monocytes to tumor antigens from the cancer. The treated monocytes cells are then transferred back into the patient with the cancer for treatment purposes (column 5, lines 34-43). Cohen et al. also teach that the dendritic cells can also be challenged with antigens from the surface of HIV-1 or other disease

carrying agents such as cancer cells of the breast, brain, liver or stomach (column 38, lines 14-25).

As noted previously, the instant claims are composition by process claims, and there is no disclosure of a feature to the claimed composition that distinguishes it from the composition of Cohen et al. Therefore, Cohen et al. anticipate the instant claimed invention.

Responses to Arguments

Applicants' arguments and Dr. Edelson's Declaration related to the above rejection in the Amendment filed on May 07, 2002 in Paper No. 13 (pages 2-9) have been fully considered.

Applicants mainly argued that the dendritic cells in the composition produced by the method described by Cohen have an increased cellular calcium concentration as compared to the dendritic cells produced by the process of the present invention, and therefore the dendritic cell composition of Cohen is inherently distinguishable from the composition of the presently claimed invention. Examiner respectfully finds Applicants' argument to be unpersuasive because is no evidence indicating that the activated myeloid dendritic cells of Cohen et al. have elevated cellular calcium concentration compared to functional dendritic antigen presenting cells produced or induced by other methods, including those containing in the composition of the presently claimed invention.

Accordingly, claims 13-23 and 64 remain rejected for the same reasons set forth above.

Claim Rejections - 35 USC § 103

Claims 24-27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Cohen et al. (U.S. Patent No. 6,010,905) or Garbe et al. (Blood 92, No. 10, Supplement 1, 165a, 1998, PTO-1449 in paper no. 4) or Tedder et al. (U.S. Patent No. 5,849,589) in view of Patel (U.S. Patent No. 5,167,657).

Claims 24-27 are directed to a packaged preparation comprising: a composition comprising functional dendritic antigen presenting cells derived from monocytes which have been incubated following their treatment by at least one of: (1) exposure to physical perturbation, (2) irradiation in the presence of a photoactivatable agent that forms photoadducts with cellular components, or (3) treatment with a DNA binding agent; and a container which does not leach plasticizer and which is sufficiently porous to permit exchange of gases for storing the composition.

Cohen et al. teach a preparation of monocytes having increasing the antigen presenting ability including those with the phenotype of an activated myeloid dendritic cell by contacting the monocytes with an agent, preferably a calcium ionophore, which elevates the intracellular calcium concentration to a level sufficient and effective to increase said antigen presenting ability (column 4, lines 13-18, column 5, lines 5-12). Cohen et al. disclose that the same composition further treated with a second agent selected from the group consisting of rhGM-CSF, rhIL-4, rhIL-12, rhIL-2, and

rhTNFalpha (column 5, lines 5-12). Cohen et al. further teach contacting the monocytes isolated from the blood of a subject with a cancer with an agent which increases the intracellular calcium concentration, thereby enhancing the antigen presenting ability of the monocytes, then exposing the monocytes to tumor antigens from the cancer. The treated monocytes cells are then transferred back into the patient with the cancer for treatment purposes (column 5, lines 34-43). Cohen et al. also teach that the dendritic cells can be challenged with antigens from the surface of HIV-1 or other disease carrying agents such as cancer cells of the breast, brain, liver or stomach (column 38, lines 14-25). Garbe et al. disclose the generation of CD1a+ dendritic cells from monocytes in the presence of IL-4, GM-CSF and TGFβ under serum-free conditions, and the phenotype of cells obtained after 7 days was determined by flow cytometry (second full paragraph, lines 1-4). Garbe et al. further teach that in the presence of both TGFβ and tetanus toxoid, the generated dendritic cells were less effective to stimulate the proliferation of primed autologous T-cells as compared to dendritic cells being depleted of TGFβ before being matured in the presence of TNF-α (second paragraph, lines 12-16). Tedder et al. disclose a composition comprising induced differentiated monocytes into dendritic cells in the presence of GM-CSF, IL-4 and TNFα (column 2, lines 19-37) at various cultured time periods (at least 5 days; see cols. 5-6). The monocytes are plastic adherent human blood monocytes (col. 2, lines 48-49). Tedder et al. disclose that upon addition of TNFα into GM-CSF and IL-4 cell cultures at day 5, the cells became adherent to the tissue culture plates and 78-95% of the cells became CD83+ within 2-3 days (col. 5, lines 28-31). Furthermore, Tedder et al. teach that the

dendritic cells are plated in cultured dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells (column 11, lines 51-57). The compositions disclosed by Cohen et al., Garbe et al. and Tedder et al. are indistinguishable from those of the instantly claimed invention. However, Cohen et al., Garbe et al. and Tedder et al. did not teach the packaging of the disclosed compositions in a container which does not leach the plasticizer and which is sufficient porous to permit exchange of gases for storing the composition.

Patel discloses the making and using of flexible, autoclavable, plastic containers for storing red blood cells and these containers are able to suppress hemolysis of the red blood cells (See Summary of the Invention, columns 2 and 3).

Accordingly, at the time of the instant invention it would have been obvious to the ordinary skilled artisan to package the compositions disclosed by Cohen et al., Garbe et al. and Tedder et al. in the plastic containers taught by Patel for storage and for later use of the activated dendritic cells to treat patients in need of. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

It is further noted that the rejection of the above claims can also be applied using the teachings of Akagawa et al. (Blood 88:4029-4039, 1996) in view of Patel (U.S. Patent No. 5,167,657).

Responses to Arguments

Applicants' arguments and Dr. Edelson's Declaration related to the above rejection in the Amendment filed on May 07, 2002 in Paper No. 13 (pages 9-10) have been fully considered.

Applicants mainly argued that the teachings of Garbe, Tedder, Akigawa or Cohen do not teach or suggest the composition of the presently claimed invention for the reasons already discussed above, and since the Patel reference does not add anything to the teachings of Garbe, Tedder, Akigawa or Cohen regarding to the compositions that are contained in the packaged preparations of the instant claims, the instant claims are unobvious over Patel in view of Garbe, Tedder, Akagawa or Cohen. Applicants' arguments regarding to the teachings of Garbe, Tedder, Akigawa or Cohen are not found to be persuasive for the reasons already discussed in the previous rejections. Therefore, the packaged preparation of the instant claimed invention as a whole would have been obvious to one of ordinary skilled in the art in light of the combined teachings of either Garbe, Tedder, Akigawa or Cohen in view of Patel.

Claims 13-27, 46-60 and 64-65 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Edelson (WO 97/34472, PTO-1449 in paper no. 2) in view of any one of Tedder et al. (U.S. Patent No. 5,849,589) or Cohen et al. (U.S. Patent No. 6,010,905) or Garbe et al. (Blood 92, No. 10, Supplement 1, 165a, 1998, PTO-1449 in paper no. 4) and Patel (U.S. Patent No. 5,167,657).

Claims 13-23 and 64 are drawn to a composition comprising functional dendritic antigen presenting cells derived from monocytes which have been incubated following their treatment by at least one of: (1) exposure to physical perturbation, (2) irradiation in the presence of a photoactivatable agent that forms photoadducts with cellular components, or (3) treatment with a DNA binding agent. Claims 46-59 and 65 are directed to a composition of co-incubated populations comprising: a first population including disease effector agents which express at least one disease associated antigen; and a second population including functional dendritic antigen presenting cells derived from monocytes which have been treated by at least one of: (1) exposure to physical perturbation, (2) irradiation in the presence of a photoactivatable agent that forms photoadducts with cellular components, or (3) treatment with a DNA binding agent; the same composition wherein the disease effector agents are selected from the group consisting of T-cell, B-cells and macrophages, and wherein the T cells include lymphoma cells, preferably cutaneous T-cell lymphoma cells; and wherein the composition further comprises at least one immunomodulatory agent. Claims 24-27 and 60 are drawn to packaged preparations comprising the above compositions in a container which does not leach plasticizer and which is sufficiently porous to permit exchange of gases for storing the composition.

Edelson teach that cultured dendritic cells can be added to or incubated with extracorporeal blood containing disease effector cells that has been treated via known photophoretic methods to increase the degree of immune responses for treating various diseases such as leukemia, lymphoma, autoimmune disease, graft versus host disease,

and transplanted tissue rejection (page 4, lines 20-28 and page 5, lines 8-12). The disease effector cells include and not limit to T cells, encompassing cutaneous T cell lymphoma, B cells, and/or infected white blood cells, such as virally or bacterially infected cells (page 5, lines 8-12 and page 2, line 4-11). Edelson further teaches that the agents that are used to treat disease effector cells include photoactivatable chemical agents such as psoralens (8-MOP), porphyrin, pyrenes, phthalocyanine; chemotherapeutic agents such as cyclophosphamide, methotrexate, cytokines including TNFalpha and interferon gamma; non-chemical agents such as UVA irradiation, X-ray irradiation, gamma-ray irradiation, and agents such as mitomycin C, cis-platinum among others (See pages 11-13 under section V). Edelson also discloses that the dendritic cells can be added or incubated with extracorporeal blood containing disease effector cells at any stage of the conventional phopheresis procedure (page 17, lines 5-11). It is also recognized that photophoresis induces the release and transfer of disease associated peptides from the treated disease effector cells to the MHC sites of the dendritic cells (page 16, lines 11-15, lines 20-23; page 22, lines 12-16). Moreover, Edelson discloses that such compositions are contained in a blood collecting bag (page 15, lines 19-28). However, Edelson does not specifically teach that functional dendritic cells in the disclosed compositions are derived from monocytes, or the time period required for the coincubation of the two cell populations to facilitate necessary direct cell to cell contact between the added dendritic cells and the treated disease effector cells or a container with recited properties.

Tedder et al. teach that monocytes can be induced to differentiate into functional dendritic cells in the presence of GM-CSF, IL-4 and TNFα in culture (column 2, lines 19-37). Furthermore, Tedder et al. teach that the dendritic cells are plated in cultured dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells (column 11, lines 51-57). Similarly, both Cohen et al. and Garbe et al. established appropriate culture conditions to induce the differentiation of monocytes, including those isolated from the blood of a patient having a cancer, into functional dendritic cells (Cohen et al., column 4, lines 13-18, column 5, lines 5-12 and lines 34-43; Garbe et al., see abstract). Patel discloses the making and using of flexible, autoclavable, plastic containers for storing red blood cells and these containers are able to suppress hemolysis of the red blood cells (See Summary of the Invention, columns 2 and 3) and have obvious properties as those recited in the claims.

Accordingly, at the time of the instant invention it would have been obvious to the ordinary skilled artisan to utilize functional dendritic cells derived from monocytes taught by Tedder et al., Cohen et al., Garbe et al. in the compositions taught by Edelson to arrive at the instant claimed invention. Furthermore, it would also have been obvious for one of ordinary skilled in the art to co-incubate the two cell populations in the disclosed compositions in an optimal period of time to allow the transfer of disease associated peptides from the treated disease effector cells to the MHC sites of the dendritic cells, and such compositions are contained in a blood collecting bag of the type taught by Patel. One of ordinary skilled in the art would have been motivated to

carry out the above modification because as taught by Edelson such compositions would improve or enhance immune responses to treat various diseases such as leukemia, lymphoma, autoimmune disease, graft versus host disease, and transplanted tissue rejection. Moreover, Edelson does not limit the use of dendritic cells derived from any particular source in his disclosed compositions (page 14, lines 26-30). Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Responses to Arguments

Applicants' arguments and Dr. Edelson's Declaration related to the above rejection in the Amendment filed on May 07, 2002 in Paper No. 13 (pages 10-11) have been fully considered.

Applicants mainly argued that "The Edelson (WO97/34472) reference does not add anything to the teachings of Garbe, Tedder, Akagawa or Cohen regarding to the compositions set forth in claims 13-27 and 46-60". Particularly, the dendritic cells used in the method disclosed by Edelson (WO97/34472) are prepared using previously known dendritic cell culture methods separately from the photospheresis treatment of the blood. Furthermore, Applicants argued "there is nothing in the Edelson (WO97/34472) reference that suggests that the method described in the Edelson '872 patent may be modified to produce functional antigen presenting dendritic cells by photospheresis". Examiner respectfully finds Applicants' arguments to be unpersuasive for the following reasons.

Firstly, it is noted that the instant claims are drawn to composition claims and not method claims. As such, the modified compositions resulting from the combined teachings of the Edelson (WO97/34472) in view of any one of Tedder, Garbe, Akagawa or Cohen and in view of Patel (U.S. Patent No. 5,167,657) would possess the same properties as those of the instant claimed compositions for the reasons set forth above, and particularly for the reasons previously discussed with regard to the teachings of Tedder, Garbe, Akagawa or Cohen.

Secondly, MPEP 2112.01 clearly states that "If the composition is physically the same, it must have the same properties". Additionally, MPEP 2112.02 clearly states that "While the references do not show a specific recognition of that result, its discovery by appellants (the induction of differentiation of monocytes into functional dendritic antigen presenting cells under photospheresis condition) is tantamount only finding a property in the old composition".

Accordingly, the claims remain rejected for the reasons set forth above.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER